Applicant : Andreas Braun *et al.*   Attorney's Docket No.: 17082-046001 (24736-2033)
Serial No. : 09/687,483   **Amendment**
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REMARKS

A check for $475 for the fee for the three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A Notice of Change of Address accompanies this response.

Claims 4, 5, 9-15, 31-34, 43, 44, 47-50, 54 and 98-125 are pending in this application. Claims 6-8, 16, 17, 45, 46 and 53 are cancelled herein without prejudice or disclaimer.

The specification is amended herein to correct an inadvertent typographical error. Claims 4, 9-15, 31, 32, 43, 47-50, 54, 98, 100, 101 and 107 are amended herein. Claims 4 and 43 are amended to more distinctly claim the subject matter by replacing the recitation "identifying healthy members of a population" with the recitation –selecting only healthy members of a population of organisms not manifesting any disease state– and replacing the recitation "identified" with the recitation –selected– throughout the claims. Basis for the amendment is found throughout the specification (*e.g.*, see page 4, lines 9-12). Claim 4 is further amended to more distinctly claim the subject matter by claiming "datapoints" that include historical information and data related to the selected individual. Basis for the amendment is found throughout the specification (*e.g.*, see claim 9 as originally filed).

Claims 9-15 and 47-50 are amended herein to more distinctly claim the subject matter to claim a method of making a database. Basis for the amendment is found throughout the specification (for example, see page 22, lines 17-29). Claim 15 is amended to spell out the abbreviations, basis for which can be found in original claim 50 as filed. Claims 15 and 50 are further amended to include the recitation –information indicative of polymorphisms–, basis for which is found throughout the specification (for example, see page 24, line 5). Claims 15, 48, 50 and 107 are amended to correct minor grammatical or formatting errors.

Claim 31 is amended to more distinctly claim the subject matter to state that the database is a healthy subject database that includes parameters for subjects in the database, basis for which is found throughout the specification (*e.g.*, see page 14, lines 4-13). Claim 31 is further amended to recite that the computer includes software for manipulating the data. Basis for the amendment is found throughout the specification (*e.g.*, see page 33, lines 2-11 and page 40, line 3 through page 43, line 25). Claim 32 is amended herein to replace the recitation "database of claim 8" with the recitation –the computer system of claim 31–, basis for which is found throughout the

specification (*e.g.*, see page 39, lines 3-8). Claim 54 is amended herein to particularly claim the subject matter to recite –a plurality of processing stations– and –the computer system of claim 31–, basis for which is found throughout the specification (*e.g.*, see claim 32 as originally filed and page 39, lines 3-8).

Claims 98 and 100 are amended herein to replace the recitation "database of claim 8" with the recitation – the computer system of claim 31–, basis for which is found throughout the specification (*e.g.*, see FIG. 24; page 10, lines 13-14; page 40, lines 9-12 and page 96, lines 4-8). Claim 101 is amended to include the recitation –the computer software enters the data analysis determination into the database–. Basis for the amendment can be found throughout the specification (for example, see page 40, lines 3-20 and page 48, lines 7-10).

Basis for new claims 109 and 122 is found throughout the specification (*e.g.*, see page 4, lines 14-17). Basis for new claim 110 is found throughout the specification (*e.g.*, see page 48, lines 4-6 and original claim 9 as filed). Basis for new claim 111 is found throughout the specification (*e.g.*, see page 14, lines 4-6). Basis for new claim 112 is found throughout the specification (*e.g.*, see page 15, lines 3-7). Basis for new claim 113 is found throughout the specification (*e.g.*, see page 20, lines 8-11). Basis for new claim 114 is found throughout the specification (*e.g.*, see page 23, lines 19-22). Basis for new claims 115 and 116 is found throughout the specification (*e.g.*, see page 15, lines 9-12 and 29-30). Basis for new claims 117-119 is found throughout the specification (*e.g.*, see page 24, lines 1-9 and original claim 15 as filed). Basis for new claim 120 is found throughout the specification (*e.g.*, see page 22, lines 18-29 and original claim 4 as filed). Basis for new claim 121 is found throughout the specification (*e.g.*, see page 22, lines 18-29, page 25, lines 9-12 and original claim 43 as filed). Basis for new claims 123-125 is found throughout the specification (*e.g.*, see page 24, lines 4-9). Therefore, no new matter is added. The amendments should place the claims and the application into condition for allowance.

THE REJECTION OF CLAIMS 6-17, 31, 45-50, 53 and 54 UNDER 35 U.S.C. §101

Claims 6-17, 31, 45-50, 53 and 54 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter because the Examiner alleges that the claimed database is only a compilation or arrangement of data and that such descriptive data is not patentable. The Examiner urges that nonfunctional descriptive material recorded on computer-readable media is not statutory subject matter because no requisite functionality is present to satisfy the practical application requirement.

ANALYSIS

Applicant respectfully submits that the rejection is rendered moot with respect to claims 6-8, 16, 17, 45, 46 and 53, which are cancelled herein without prejudice or disclaimer. The rejection is obviated with respect to claims 9-13, 15 and 47-50, which are amended herein to recite methods of producing databases, and thus are not directed to a database *per se*. The claimed methods include manipulation of data representing physical objects or activities, and performance of independent acts (such as identifying a healthy population, collection of data and samples for identified members, and analyzing the samples), and each produces a tangible concrete product – a healthy subject database.

Applicant respectfully submits that the rejection is obviated with respect to claim 31 in light of the amendment herein. Claim 31 is are not directed to a database *per se*, but is directed to a computer system that includes a computer with software in computer memory for manipulating a healthy subject database, where the software includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Applicant respectfully submits that claim 31 and claims depending therefrom are computer-related product claims. The USPTO has formulated and published guidelines for Examiners to use when examining computer-related inventions (Examination Guidelines for Computer-Related Inventions, Final Version, published in the February 28, 1996 Federal Register (61 Fed. Reg. 7478), parts of which are included in the MPEP as Chapter 2106). MPEP 2106(IV)(2)(a) discusses statutory product claims and states

> If a claim defines a useful machine or manufacture by identifying the physical structure of the machine or manufacture in terms of its hardware or hardware and software combination, it defines a statutory product. See, *e.g., Lowry*, 32 F.3d at 1583, 32 USPQ2d at 1034-35; *Warmerdam*, 33 F.3d at 1361-62, 31 USPQ2d at 1760.

The Examiner's attention is directed to Examination Guidelines Section IV(B)(2)(a)(i), which states in pertinent part that:

> Office personnel must treat each claim as a whole. . . . If a product claim encompasses any and every computer implementation of a process, when read in light of the specification, it should be examined on the basis of the underlying process. Such a claim can be recognized as it will:
>
> - define the physical characteristics of a computer or computer
>   component exclusively as functions or steps to be performed on or by a computer, and

- encompass any and every product in the stated class (*e.g.*, computer, computer-readable memory) configured in any manner to perform that process.

. . .

When Office personnel have reviewed the claim as a whole and found that it is not limited to a specific machine or manufacture, they shall identify how each claim limitation has been treated [].

If a claim is found to encompass any and every product embodiment of the underlying process, and if the underlying process is statutory, the product claim should be classified as a statutory product. By the same token, if the underlying process invention is found to be non-statutory, Office personnel should classify the "product" claim as a "non-statutory product." If the product claim is classified on the basis of the underlying process, Office personnel should emphasize that they have considered all claim limitations and are basing their finding on the analysis of the underlying process.

It is respectfully submitted that the claimed subject matter is not limited to a specific machine or manufacture, but is intended to encompass any and every product embodiment of the underlying process. Thus, the claims must be treated as a whole. The Examiner's attention is directed to MPEP 2106(B):

Accordingly, Office personnel should begin their evaluation of a computer-related invention as follows:
- determine what the programmed computer does when it performs the processes dictated by the software (*i.e.*, the functionality of the programmed computer);
- determine how the computer is to be configured to provide that functionality (*i.e.*, what elements constitute the programmed computer and how those elements are configured and interrelated to provide the specified functionality); and
- if applicable, determine the relationship of the programmed computer to other subject matter outside the computer that constitutes the inventions (*e.g.*, machines, devices, materials, or process steps other than those that are part of or performed by the programmed computer.

Applicant respectfully submits that the programmed computer determines the frequency of datapoints as a function of a selected parameter in the population. Changes in the frequency of the parameter when the healthy subject database is stratified according to a different parameter can be used to identify or discover polymorphisms and genetic markers. The instant application provides a way to identify allelic variants and polymorphisms, and other methods, such as identifying candidate genetic markers and discovery of a polymorphism in a population, which do not require a comparison to diseased subjects. Once the allelic variants and polymorphisms are identified, they can be associated with disease. By collecting data from healthy members of a population and entering it into a database, the data can be stratified

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according to selected parameters, such as age, ethnicity or sex, and information emerges. The information allows for correlating a marker or polymorphism with a pre-determined parameter. For example, the data on the lipoprotein lipase gene in the healthy subject database can be sorted according to age, ethnicity and sex to determine changes in frequency of the gene against these parameters. The results show a decrease in the frequency of the allele with age in males but no such decrease in females (see Figures 2A-2C). Other alleles that have been tested using the database include alleles of p53, p21 and factor VII, and the results when sorted by age are shown in the Figures.

These examples demonstrate an altered frequency of disease-causing genetic factors within the general population. The scientific interpretation of these results allows prediction of medical relevance of polymorphic genetic alterations. In addition, conclusions can be drawn with regard to their penetrance, diagnostic specificity, positive predictive value, onset of disease, most appropriate onset of preventive strategies and the general applicability of genetic alterations identified in isolated populations to panmixed populations (see page 34). For example, Example 1 describes the use of a database containing information provided by a population of healthy individuals not manifesting any disease state to determine the distribution of allelic frequencies of known genetic markers with age and by sex in a Caucasian subpopulation of the database. The results described in the Example demonstrate that a disease-related genetic marker or polymorphism can be identified by sorting a healthy subject database by a parameter or parameters, such as age, sex and ethnicity.

The traditional strategy to identify polymorphisms valuable to an understanding of disease is cumbersome and dependent upon the availability of many large patient and control groups to show some association between the polymorphism and disease. Such an approach may not be able to identify many polymorphisms that have a clinical relevance or utility. For example, genes that cause a general risk of the population to suffer from any disease (morbidity susceptibility genes) will escape these case/control studies entirely (page 38, lines 22-26).

The healthy subject databases and systems disclosed in the application use a strategy to identify polymorphisms that does not require comparison to a diseased population. The instant application provides methods to identify polymorphisms and other markers that may be related to a pre-determined parameter, such as age, sex or ethnicity, without prior knowledge of their existence, by stratifying information in healthy subject databases (information from individuals selected only on the basis of being healthy) according to pre-determined parameters. The basic

method is to stratify a database of information from healthy subjects according to a pre-determined parameter, such as age, and to identify any markers whose frequency changes as a function of the parameter. Any marker that exhibits a statistically significant frequency change as a function of the parameter is a candidate for further investigation.

In *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368, 47 USPQ2d 1596 (Fed. Cir. 1998) it was found that as long as the computer program, method or process "produces a useful, concrete and tangible result" then the claimed subject matter is patentable:

> Today, we hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"—a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades. The district court erred by applying the Freeman-Walter-Abele test to determine whether the claimed subject matter was an unpatentable abstract idea. The Freeman-Walter-Abele test was designed by the Court of Customs and Patent Appeals, and subsequently adopted by this court, to extract and identify unpatentable mathematical algorithms in the aftermath of *Benson* and *Flook*. See *In re Freeman*, 573 F.2d 1237, 197 USPQ 464 (CCPA 1978) as modified by *In re Walter*, 618 F.2d 758, 205 USPQ 397 (CCPA 1980). The test has been thus articulated:
>
> > First, the claim is analyzed to determine whether a mathematical algorithm is directly or indirectly recited. Next, if a mathematical algorithm is found, the claim as a whole is further analyzed to determine whether the algorithm is "applied in any manner to physical elements or process steps," and, if it is, it "passes muster under § 101." *In re Pardo*, 684 F.2d 912, 915, 214 USPQ 673, 675-76 (CCPA 1982) (citing *In re Abele*, 684 F.2d 902, 214 USPQ 682 (CCPA 1982)).

Applicant respectfully asserts that claim 31 encompasses a computer and software for manipulating data representing physical objects or activities (pre-computer activity) and produces a tangible concrete product – a frequency of the parameter. The frequency of the parameter constitutes the transformation of data in the healthy subject database into "a useful, concrete and tangible result" – a number that is useful, for example, for the discovery of polymorphisms and the correlation of polymorphisms to disease as described in the instant specification. Hence, claim 31 is directed to statutory subject matter.

THE REJECTION OF CLAIMS 4-17, 31, 43-50 and 53 UNDER 35 U.S.C. § 102(b)

Claims 4-17, 31, 43-50 and 53 are rejected under 35 U.S.C. § 102(b) as anticipated by Campbell *et al.* (WO 98/35609) because that reference allegedly discloses a computer-based system for predicting the future health of an individual based upon acquiring and analyzing a number of biological and physiological biomarkers. The Examiner urges that the database of Campbell *et al.* is a "healthy database" because the instant claims do not include a limitation stating "excluding the most severely diseased" from the healthy database, and the database of Campbell *et al.* takes samples from a large population and includes all ranges of health.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. *See, also, Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 4 is directed to a method of producing a database that includes selecting only healthy members of a population of organisms not manifesting any disease state; obtaining data comprising identifying information and obtaining datapoints comprising historical information and data relating to the selected members of the population and their immediate family; entering the data and datapoints for each member of the population into a database; associating the respective data and datapoints of the individual member with an indexer; and storing the database on a computer-readable medium.

Claim 31 is directed to a computer system that includes a healthy subject database and a computer that includes software for manipulating the database, where a include data from a population in which each individual is a healthy subject and a healthy subject is a subject who does not manifest a disease state; the data includes parameters for subjects in the database; and the computer software includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Claim 43 is directed to a method of producing a database stored in a computer memory that includes selecting healthy members of a population not manifesting any disease state; obtaining identifying and historical information and data relating to the identified members of the population; and entering the member-related data into the computer memory database for each identified member of the population and associating the member and the data with an indexer, wherein the database is a relational database.

ANALYSIS

Applicant respectfully submits that the rejection is rendered moot with respect to claims 6-8, 16, 17, 45, 46 and 53, which are cancelled herein without prejudice or disclaimer.

DISCLOSURE OF CAMPBELL *et al.*

Campbell *et al.* discloses a system for predicting the future health of an individual that includes (1) a computer containing a database based on biomarkers of a test population D (identified as having acquired a specific condition within a specified time or age interval) and sub-population $\bar{D}$ (identified as not having acquired the condition within the specified parameter), and (2) a computer program that manipulates the data in the database. More particularly, the system and method predicts the future health of an individual in a risk group by comparing an individual's profile of biomarkers (such as serum cholesterol) with biomarker values obtained from members of a large test population. Campbell *et al.* discloses a computer-based method for assessing future health risks for a specific individual and for monitoring the preventative measures taken so as to reduce future health risks for that specific individual (page 6, lines 26-29). Campbell *et al.* discloses a computer program that includes steps for applying a statistical procedure to the biomarkers to classify an individual as having a high probability of acquiring a specified biological condition (page 8, lines 2-7).

Differences between the claimed subject matter and the disclosure of the Campbell *et al.*

Independent claims 4 and 43 and their dependent claims are directed to methods of producing a database, which include as an element selecting only healthy members of a

population of organisms not manifesting any disease state. Claim 31 is directed to a computer system that includes a healthy subject database and software for manipulating the healthy database. Thus, all of claims 4, 5, 9-15, 17, 31, 43, 44 and 47-50 include as an element a database produced by a method that includes selecting only healthy members of a population of organisms not manifesting any disease state.

The traditional strategy to identify polymorphisms valuable to an understanding of disease is cumbersome and dependent upon the availability of many large patient and control groups to show some association between the polymorphism and disease. Such an approach may not be able to identify many polymorphisms that have a clinical relevance or utility. For example, genes that cause a general risk of the population to suffer from any disease (morbidity susceptibility) will escape these case/control studies entirely (page 38, lines 22-26).

The specification teaches on page 20, lines 17-29 that:

> The traditional approach is based on the concept that the onset and/or progression of diseases can be correlated with the presence of a polymorphisms or other genetic markers. This approach does not consider that disease correlated with the presence of specific markers and the absence of specific markers. It is shown herein that identification and scoring of the appearance and disappearance of markers is possible only if these markers are measured in the background of healthy subjects where the onset of disease does not mask the change in polymorphism occurrence. Databases of information from disease populations suffer from small sample size, selection bias and heterogeneity. The databases provided herein from healthy populations solve these problems by permitting large sample bands, simple selection methods and diluted heterogeneity.

The specification discloses a strategy to identify polymorphisms using the healthy subject database that does not require comparison to a diseased population. As discussed above, the instant application provides methods to identify polymorphisms and other markers that may be related to a pre-determined parameter, such as age, sex or ethnicity, without prior knowledge of their existence, by stratifying information in healthy subject databases (information from individuals selected only on the basis of being healthy) according to pre-determined parameters. Any marker that exhibits a statistically significant frequency change as a function of the parameter is a candidate for further investigation.

As claimed, claims 4, 5, 9-15, 17, 31, 43, 44 and 47-50 include a healthy database that includes data from only healthy members of a population of organisms not manifesting any disease state. The database of biomarkers disclosed by Campbell *et al.* includes all ranges of health, from the most robustly healthy to the most severely diseased (page 22, lines 14-15).

Campbell *et al.* does not disclose selecting only healthy members of a population of organisms not manifesting any disease state.

Hence, Campbell *et al.* does not disclose a method of producing a database that includes as an element selecting only healthy members of a population not manifesting any disease state, or a system that includes a database that includes as an element selecting only healthy members of a population not manifesting any disease state. Thus, Campbell *et al.* does not disclose every element of the instant claims. Therefore, because Campbell *et al.* does not disclose all elements of the claimed subject matter, Campbell *et al.* does not anticipate any of claims 4-17, 31, 43-50 and 53.

REJECTION OF CLAIMS 32-34, 99, 100 AND 102 UNDER 35 U.S.C. § 103(a)

Claim 32-34, 99, 100 and 102 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bullaughey *et al.* (EP 0596205 A2, 1994) in view of Campbell *et al.* (WO 98/35609) in further view of Vestal (US 5,498,545) because Bullaughey *et al.* allegedly teaches an automated bench supervisor system that includes every element of the claimed subject matter except the database of claim 8 and a data analysis system, but Campbell *et al.* and Vestal allegedly cures these defects.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to

fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.*L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 32 is directed to a system for high throughput processing of samples that includes a process line, a robotic system for transport along the process line, a data analysis system that automatically processes the test results to make a determination regarding the biological sample, a control system and the computer system of claim 31, which, as discussed above, includes a healthy subject database and software for manipulating the database. Claims 33 and 34 depend from claim 32 and are directed to various embodiments thereof.

Claim 99 depends from claim 98 and is directed to a combination of the computer system of claim 31 and a mass spectrometer, where the combination is an automatic process line for analyzing biological samples.

Claim 100 is directed to a system for high throughput processing of biological samples that includes an automated process line that includes a plurality of processing stations, each of which performs a procedure on a biological sample contained in a reaction vessel, the computer system of claim 31 and a mass spectrometer.

Claim 102 depends from claim 101, and is directed to an embodiment thereof where the method requires one of the processing stations to be a mass spectrometer.

TEACHINGS OF THE CITED REFERENCES

Bullaughey *et al.*

Bullaughey *et al.* is directed to an analytical system (a Bench Supervisor system) that coordinates the operations of various hardware instruments in carrying out a bench method or bench sequence and communicates with a number of instrument applications or programs.

Campbell *et al.*

See related section above.

Vestal

Vestal teaches a system for analyzing multiple samples by MALDI-MS. The system includes portable sample supports to accommodate a plurality of samples. A robotic transport mechanism is provided for automatically inputting and outputting each of the sample supports from the sample receiving chamber of a mass spectrometer. A computer is also provided for recording test data from the mass spectrometer and for controlling the operation of the system.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Bullaughey *et al.* with the teachings of Campbell *et al.* and Vestal does not result in the instantly claimed subject matter.

Claims 32-34

Bullaughey *et al.* teaches an analytical system that coordinates the operations of various hardware instruments in carrying out a lab bench method and communicates with a number of instrument applications or programs. Bullaughey *et al.* does not teach or suggest a healthy subject database that includes data from only healthy members of a population of organisms not manifesting any disease state or computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Campbell *et al.* does not cure these defects. Campbell *et al.* teaches a system for predicting the future health of an individual that includes a computer containing a database based on biomarkers of a test population D and sub-population $\bar{D}$ and a computer program that manipulates the data in the database. Campbell *et al.* does not teach or suggest a database where the data included therein is only from healthy members of a population not manifesting any disease state. As discussed above, the database of Campbell *et al.* teaches a database that includes the most severely diseased members of a population. Campbell *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, the combination of the teachings of Bullaughey and Campbell *et al.* does not teach or suggest every element of claim 32.

Vestal does not cure these defects. Vestal teaches a system for analyzing multiple samples by MALDI-MS. The system includes portable sample supports, each able to accommodate a plurality of samples. A computer also is provided for recording test data from the mass spectrometer and for controlling the operation of the system. Vestal does not teach or suggest a healthy subject database that includes data from only healthy members of a population of organisms not manifesting any disease state. Vestal does not teach or suggest software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Thus, combining the teachings of Vestal with the teachings of Bullaughey or Campbell *et al.* or with the combined teachings of Bullaughey and Campbell *et al.* does not teach or suggest every element of claim 32. None of Bullaughey, Campbell *et al.* nor Vestal, individually or in any combination, teaches or suggests every element of claims 32-34. Therefore, because combining the teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 99

Claim 99 depends from claim 98 and is directed to a combination of the computer system of claim 31 and a mass spectrometer, where the combination is an automatic process line for analyzing biological samples.

Bullaughey *et al.* teaches an analytical system that coordinates the operations of various hardware instruments in carrying out a lab bench method and communicates with a number of instrument applications or programs. Bullaughey *et al.* does not teach or suggest a database that includes data from only healthy members of a population not manifesting any disease state. Bullaughey *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Campbell *et al.* does not cure this defect. Campbell *et al.* does not teach or suggest a database that includes data from only healthy members of a population not manifesting any disease state. As discussed above, the database taught by Campbell *et al.* includes all ranges of health, from the most robustly healthy to the most severely diseased. Campbell *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Bullaughey *et al.* and Campbell *et al.* does not teach or suggest every element of claim 99.

Vestal does not cure these defects. Vestal teaches a system for analyzing multiple samples by MALDI-MS. Vestal does not teach or suggest a healthy subject database that includes data from only healthy members of a population of organisms not manifesting any disease state. Vestal does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Vestal with the teachings of Bullaughey *et al.* or Campbell *et al.* or with the combined teachings of Bullaughey *et al.* and

Campbell *et al.* does not teach or suggest every element of claim 99. None of Bullaughey *et al.*, Campbell *et al.* or Vestal, individually or in any combination, teaches or suggests every element of the subject matter of claim 99. Therefore, because the combination of teachings of the references does not result in the subject matter of claim 99, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 100

Claim 100 is directed to a system for high throughput processing of biological samples that includes an automated process line that includes a plurality of processing stations, each of which performs a procedure on a biological sample contained in a reaction vessel, the computer system of claim 31 and a mass spectrometer.

Bullaughey *et al.* teaches an analytical system that coordinates the operations of various instruments in a lab bench method that communicates with a number of instrument applications or programs. Bullaughey *et al.* does not teach or suggest a database that includes data from only healthy members of a population not manifesting any disease state. Bullaughey *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Campbell *et al.* does not cure this defect. Campbell *et al.* does not teach or suggest a database that includes data from only healthy members of a population not manifesting any disease state. As discussed above, the database taught by Campbell *et al.* includes all ranges of health, from the most robustly healthy to the most severely diseased. Campbell *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Bullaughey *et al.* and Campbell *et al.* does not teach or suggest every element of claim 100.

Vestal does not cure these defects. Vestal teaches a system for analyzing multiple samples by MALDI-MS. Vestal does not teach or suggest a healthy subject database that includes only healthy members of a population of organisms not manifesting any disease state. Vestal does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Vestal with the teachings of Bullaughey *et al.* or Campbell *et al.* or with the combined teachings of

Bullaughey *et al.* and Campbell *et al.* does not teach or suggest every element of claim 100. None of Bullaughey *et al.*, Campbell *et al.* or Vestal, individually or in any combination, teaches or suggests every element of the subject matter of claim 100. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a prima facie case of obviousness.

Claim 102

Claim 102 depends from claim 101, and is directed to an embodiment thereof where the method requires the mass spectrometer of the process line to use a spectrometric format selected from among Matrix-Assisted Laser Desorption/Ionization, Time-of-Flight (MALDI-TOF), Electrospray (ES), IR-MALDI, Ion Cyclotron Resonance (ICR), Fourier Transform and combinations thereof. Claim 101 requires as an element transporting a reaction vessel along the system of claim 32.

As discussed above, the combination of the teachings of Bullaughey *et al.* and Campbell *et al.* and Vestal does not teach or suggest every element of claim 32. None of Bullaughey *et al.*, Campbell *et al.* or Vestal, individually or in any combination, teaches or suggests a system for high throughput processing of biological samples that includes a computer system as claimed in claim 31, which includes a database that includes data from only healthy members of a population not manifesting any disease state and computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Thus, combining the teachings of Bullaughey *et al.* and Campbell *et al.* and Vestal does not teach or suggest every element of claim 101. Thus, none of Bullaughey *et al.*, Campbell *et al.* or Vestal, individually or in any combination, teaches or suggests every element of the subject matter of claim 102, which depends from claim 101. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a prima facie case of obviousness.

REJECTION OF CLAIMS 54 AND 101 UNDER 35 U.S.C. § 103(a)

Claims 54 and 101 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bullaughey *et al.* (EP 0596205 A2, 1994) in view of Campbell *et al.* (WO 98/35609) because Bullaughey *et al.* allegedly teaches an automated bench supervisor system that includes every element of the claimed subject matter except the database of claim 8, but Campbell *et al.* allegedly cures these defects.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 54 is directed to an automated process line that includes a plurality of processing stations and the computer system of claim 31.

Claim 101 is directed to a method for high throughput processing of biological samples that includes transporting a reaction vessel along a system of claim 32, which includes a process line having a plurality of processing stations, each of which performs a procedure on one or more biological samples contained in the reaction vessel; determining when the test procedure at each processing station is complete and, in response, moving the reaction vessel to the next processing station; receiving test results of the process line; automatically processing the test results to make a data analysis determination regarding the biological samples in the reaction vessel; and processing reaction vessels continuously one after another until receiving a stop instruction, where the computer software enters the data analysis determination into the database.

TEACHINGS OF THE CITED REFERENCES

Bullaughey *et al.*

See related section above.

Campbell *et al.*

See related section above.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Bullaughey *et al.* with the teachings of Campbell *et al.* does not result in the instantly claimed subject matter.

Claim 54

Claim 54 is directed to an automated process line that includes a plurality of processing stations; and the computer system of claim 31, which includes a healthy subject database that includes data from only healthy members of a population not manifesting any disease state and computer software for manipulating the database that includes as an

executable step determining the frequency of datapoints as a function of a selected parameter in the population. Bullaughey *et al.* teaches an analytical system that coordinates the operations of various hardware instruments in carrying out a lab bench method and communicates with a number of instrument applications or programs. Bullaughey *et al.* does not teach or suggest a database that includes data from only healthy members of a population not manifesting any disease state. Bullaughey *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Campbell *et al.* does not cure this defect. Campbell *et al.* does not teach or suggest a healthy subject database that includes data from only healthy members of a population not manifesting any disease state. As discussed above, the database taught by Campbell *et al.* includes all ranges of health, from the most robustly healthy to the most severely diseased. Campbell *et al.* does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Bullaughey *et al.* and Campbell *et al.* does not teach or suggest every element of claim 54. Neither Bullaughey *et al.* nor Campbell *et al.*, individually or in combination, teaches or suggests every element of the subject matter of claim 54. Hence, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 101

Claim 101 is directed to a method for high throughput processing of biological samples that includes as an element transporting a reaction vessel along a system of claim 32. As discussed above, the combination of the teachings of Bullaughey *et al.* and Campbell *et al.* does not teach or suggest every element of claim 32. Neither Bullaughey *et al.* nor Campbell *et al.*, individually or in combination, teaches or suggests a system for high throughput processing of biological samples includes a healthy database as instantly claimed.

Therefore, because the combination of teachings of Bullaughey *et al.* and Campbell *et al.* does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIM 98 UNDER 35 U.S.C. § 103(a)

Claim 98 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Campbell *et al.* (WO 98/35609) in view Vestal (U.S. 5,498,545) because the Examiner alleges that Campbell *et al.* teaches the use of a computer-based system for predicting the future health of an individual based upon acquiring and analyzing a number of biological and physiological biomarkers, but fails to specifically teach the use of the database with a mass spectrometer or an automated process line that would be used for data gathering, and the Examiner contends that Vestal cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 98 is directed a combination that includes the computer system of claim 31 and a mass spectrometer.

TEACHINGS OF THE CITED REFERENCES

Campbell *et al.*

See related section above.

Vestal

See related section above.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Campbell *et al.* with the teachings of Vestal does not result in the instantly claimed subject matter.

Claim 98 includes as elements a mass spectrometer and the computer system of claim 31, which includes a healthy subject database that includes data from only healthy members of a population not manifesting any disease state and computer software for manipulating the database that includes as an executable step determining the frequency of a parameter. Campbell *et al.* does not teach or suggest a database produced by a method that includes selecting only healthy members of a population not manifesting any disease state. As discussed above, the database taught by Campbell *et al.* includes all ranges of health, from the most robustly healthy to the most severely diseased. Campbell *et al.* does not teach or

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suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Vestal does not cure this defect. Vestal teaches a system for analyzing multiple samples by MALDI mass spectrometry. Vestal does not teach or suggest a healthy subject database that includes data from only healthy members of a population not manifesting any disease state. Vestal does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, combining the teachings of Campbell *et al.* and Vestal does not teach or suggest every element of claim 98. Neither Campbell *et al.* nor Vestal, individually or in combination, teaches or suggests every element of the subject matter of claim 98. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 103-108 UNDER 35 U.S.C. § 103(a)

Claims 103-108 are rejected under 35 U.S.C. § 103(a) over Bullaughey *et al.* (EP 0596205 A2, 1994) in view of Campbell *et al.* (WO 98/35609) in view of Vestal (US 5,498,545) and in further view of Köster *et al.* (U.S. 6,043,031) because the Examiner alleges that the combination of Bullaughey *et al.* and Campbell *et al.* and Vestal teaches every element of the claimed subject matter except analysis by primer oligo base extension, and the Examiner contends that Köster *et al.* cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 103 ultimately depends from claim 101, and is directed to a method for high throughput processing of biological samples that includes a mass spectrometer as one of the processing stations and analyzing the samples by a method that includes primer oligo base extension (PROBE). Claims 104-108 depend from claim 103 and are directed to various embodiments thereof.

TEACHINGS OF THE CITED REFERENCES

Bullaughey *et al.*

See related section above.

Campbell *et al.*

See related section above.

Vestal

See related section above.

Köster *et al.*

Köster *et al.* teaches a mass spectrometer-based process for detecting a particular nucleic acid sequence in a biological sample.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

The combination of teachings of Bullaughey *et al.* **with the teachings of Campbell** *et al.* **and Vestal and Köster** *et al.* **and does not result in the instantly claimed subject matter.**

Claim 103 depends from claim 101 and includes every element recited therein. Claim 101 includes as elements transporting a reaction vessel along the system of claim 32, and as discussed above, the combination of the teachings of Bullaughey *et al.* and Campbell *et al.* and Vestal does not teach or suggest the system of claim 32. None of Bullaughey *et al.*, Campbell *et al.* or Vestal, individually or in any combination, teaches or suggests a computer system that includes a healthy subject database that includes data from only healthy members of a population not manifesting any disease state and computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population.

Köster *et al.* does not cure these defects. Köster *et al.* teaches a mass spectrometer-based process for detecting a particular nucleic acid sequence in a biological sample. Köster *et al.* does not teach or suggest a healthy subject database that includes data from only healthy members of a population not manifesting any disease state. Köster et al. does not teach or suggest computer software for manipulating the database that includes as an executable step determining the frequency of datapoints as a function of a selected parameter in the population. Thus, even if Köster *et al.* teaches analyzing samples by primer oligo base extension (PROBE), combining the teachings of Bullaughey *et al.* and Campbell *et al.* and Vestal and Köster *et al.* does not teach or suggest every element of claim 101, from which claim 103 depends. None of Bullaughey *et al.*, Campbell *et al.*, Vestal or Köster *et al.*, individually or in any combination, teaches or suggests every element of the subject matter of claims 103 or its dependent claims.
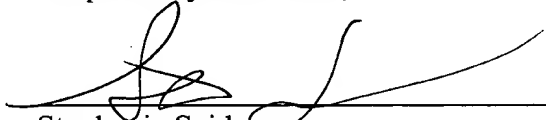
Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter of claims 103-108, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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